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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/775,479	02/02/2001	Guy Leclerc	50018 CIP	8765

7590 02/26/2003

David S. Resnick
Nixon Peabody LLP
101 Federal Street
Boston, MA 02110-1832

EXAMINER	
LAMBERTSON, DAVID A	
ART UNIT	PAPER NUMBER
1636	

DATE MAILED: 02/26/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/775,479	LECLERC ET AL.	
	Examiner	Art Unit	
	David A Lambertson	1636	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *09 December 2002* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *27-32* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *27-32* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on _____ is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) *11* .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☒ Other: *Notice to Comply* .

DETAILED ACTION

Election/Restrictions

Applicant's election of Group VIII in Paper No. 10, filed December 9, 2002 is acknowledged. Because applicant did not distinctly and specifically point out the supposed errors in the restriction requirement, the election has been treated as an election without traverse (MPEP § 818.03(a)).

In response to the Restriction requirement mailed October 3, 2002 as Paper No. 8, applicant has also elected to cancel all of the previously pending claims (1-26) in favor of the examination of newly added claims 27-32. This request is acknowledged, and claims 27-32 have been examined on the merits in the following Office Action. The election of these claims is also considered to be without traverse, since the Examiner is in agreement that the claims as added are encompassed within Group VIII a per the initial Restriction requirement.

Priority

Applicant's claim for domestic priority to US Application 09/318,106, International Application PCT/CA97/00892 (Publication WO 98/23299), and US Application 08/756,728 (now US Patent No. 5,821,354) under 35 U.S.C. 120 is acknowledged.

Information Disclosure Statement

The information disclosure statement filed with the instant application and referring to references as supplied in US Application 09/318,106 has been considered, and a signed and initialed copy is attached to this Office Action.

Drawings

The drawings as filed have been accepted by the Draftsperson.

Sequence Compliance

This application contains sequence disclosures that are encompassed by the definitions for nucleotide and/or amino acid sequences set forth in 37 C.F.R. 1.821(a)(1) and (a)(2). However, this application fails to comply with the requirements of 37 C.F.R. 1.821-1.825. Specifically, Figure 3 contains two nucleotide sequences that are not identified by SEQ ID NOS, and which are not listed in the sequence listing. Applicant is required to provide a new sequence listing, both the paper copy and computer readable format (CRF), including all sequences encompassed by the definitions set forth in 37 C.F.R. 1.821(a)(1) and (a)(2). In addition, applicant must provide a statement indicating the paper copy and CRF are the same, and that they do not incorporate new matter into the instant specification. Finally, applicant is required to amend the specification to clearly identify the sequences in Figure 3 with their appropriate SEQ ID NO. Applicant is advised that the sequences present in the Figures can be identified in the Brief Description of the Drawings, provided the indication is clear.

In this instance, the nature of the non-compliance with 37 C.F.R. 1.821-1.825 does not preclude the examination of the application on the merits, the results of which are communicated below. However, failure to comply with all of the requirements of 37 C.F.R. 1.821-1.825 in response to this Office Action will be considered non-responsive.

Specification

The disclosure is objected to because of the following informalities: Applicant should update the publication status of PCT/CA97/00892 (Publication WO 98/23299) in the first line of the specification, as amended. In addition, some minor errors appear to occur in the specification: on page 10, line 29, "contradiction" appears to be misspelled; on page 23, line 32, it appears that the indication of labeling on residue "A" should actually read on the labeling of residue "C" in the eighth position.

Appropriate correction is required.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 27-32 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

The test of enablement is whether one skilled in the art could make and use the claimed invention from the disclosures in the specification coupled with information known in the art without undue experimentation (*United States v. Telectronics.*, 8 USPQ2d 1217 (Fed. Cir. 1988)). Whether undue experimentation is needed is not based upon a single factor but rather is a conclusion reached by weighing many factors. These factors were outlined in *Ex parte*

Forman, 230 USPQ 546 (Bd. Pat. App. & Inter. 1986) and again in *In re Wands*, 8 USPQ2d 1400 (Fed. Cir. 1988) and include the following:

Nature of the invention. The nature of the invention is a method of inhibiting restenosis in an animal by supplying the animal with an internally labeled radioactive oligonucleotide, thereby ablating the proliferative cells by prolonged exposure to beta-emissions form the isotope. Applicants provide *in vivo* data concerning a porcine model, particularly regarding the balloon overstretch model of angioplasty induced-injury. The determined real-world use for this method would be a method of treating humans for restenosis following a balloon angioplasty.

Scope of the invention. The scope of the invention encompasses all animals, including humans.

State of the art. The state of the art concerning the use of animal models for a prediction of function in humans is clearly established in O'Sullivan *et al.* (*Heart* **86**: 491-493, November 2001; see the entire reference; henceforth O'Sullivan). Although this article mainly concerns gene therapy techniques with regard to restenosis, the article is analogous to subject matter concerning the use of animal models to predict function in humans with regard to treatment of restenosis (see for example the section on "*Differences between Animals and Humans*" on pages 1-2 of the provided reference). Specifically, O'Sullivan indicates that animal models for restenosis, including the commonly used rabbit, rodent and porcine models, are not predictive of function in humans for several reasons. First, the animals are sacrificed within 28 days (as they are in the instant specification), which is prior to the onset of restenosis in humans. Second, the injuries sustained in the models are not considered to be correlated to injuries that are sustained in humans. When considering the prior art as it concerns the invention, the skilled artisan would encounter teachings that indicate the unpredictable and difficult nature of the claimed invention,

thus the skilled artisan would not be able to turn to the prior art for assistance in practicing the method for its real-world use.

Number of working examples and Guidance provided by applicant. Applicants have provided *in vivo* data concerning the invention only with regards to an animal (porcine) model. Applicant presumes a functional correlation between the animal data and human application, without providing a nexus between the two elements. Furthermore, in an article published by applicant in *Cardiovascular Radiation Medicine* **2**(1): 51 (Fareh, *et al.*, 2001; see entire reference), applicant asserts that this strategy of coronary restenosis prevention requires further investigation. When practicing the instant invention for its real-world use, the skilled artisan would be unable to turn to the instant specification for guidance because there is no indication of its function in humans by way of direct results, or by a viable nexus correlating the findings in the animal models with those one would predict in humans.

Level of skill in the art. The level of skill in the art concerning using internally radiolabled oligonucleotides for the inhibition of restenosis in humans is highly underdeveloped, considering both the instant specification and the state of the art.

Unpredictability of the art. The art is highly unpredictable. This is clearly demonstrated in the state of the art, where O'Sullivan indicates that porcine models are not indicative of function in humans (see the pages referenced above under **State of the Art**). That point established, there are additional areas of unpredictability, such as the A) toxicity of the oligonucleotides to cells not undergoing restenosis, B) effective targeting of the oligonucleotides to cells undergoing restenosis, and C) the long-term effects of the oligonucleotides as it concerns restenosis. Because the animals used in the models described in the instant specification are sacrificed after

28 days, it is impossible to know if the oligonucleotides are inducing harmful side effects on the animal. For the same reason, it is impossible to ascertain how effective the treatment is in the long term. After all, the purpose of the invention is to overcome the shortcomings of the current treatments, one of which is a relapse of the blockage following angioplasty that results from restenosis. Since the relapse event usually occurs 3-6 months following the angioplasty (see page 3, line 3-6 of the instant specification) and the animals in the model used in the instant specification are sacrificed prior to said time, the skilled artisan could not determine if the invention accomplishes its goals. Finally, there is no indication in the instant specification of how to selectively target cells undergoing restenosis (with a particular antibody to an expressed cellular receptor, for example), therefore it is unpredictable as to how selective the cellular ablation will be. Each of these elements contributes to the unpredictability of the invention, which is compounded by the state of the prior art, the deficiencies of the instant specification, and the underdeveloped nature of the art.

Amount of experimentation required. There is a great deal of trial and error experimentation associated with the instant invention. First, there needs to be a bona fide correlation between the invention and its effectiveness in humans, either by experimental data or by clear indication that the animal model is predictive. Second, the toxicity, targeting and long-term effects of the treatment need to be clearly established in order to teach the skilled artisan how to use the invention. Because these elements have not been satisfied, the skilled artisan would be required to practice undue and unpredictable trial and error experimentation with regard to determining these factors. Therefore, the instant specification is not enabling for the claimed invention as determined by the above Wands factor analysis.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 27-32 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 27 recites the limitation that the sequence can be "bounded to an antibody." It is not immediately clear what applicant is indicating with this terminology as it is not clearly set forth in the specification. For example, it is unclear if the antibody is bound covalently, ionic through interaction, through hydrophobic interactions, etc. The specification does read on an oligonucleotide that has been "conjugated to an antibody", therefore amending the claim to read "DNA sequence conjugated to an antibody" would be remedial.

Allowable Subject Matter

No claims are allowable.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to David A Lambertson whose telephone number is (703) 308-8365. The examiner can normally be reached on 8am-4:30pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Remy Yucel, Ph.D. can be reached on (703) 305-1998. The fax phone numbers for

the organization where this application or proceeding is assigned are (703) 305-3014 for regular communications and (703) 305-3014 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 308-0196.

David A. Lambertson
February 24, 2003

PATENT EXAMINER
Gerald G. Leffers Jr.
A.U. 1636

Notice to Comply	Application No. 09/775479	Applicant(s) Leclerc *et al.*	
	Examiner David A. Lambertson	Art Unit 1636	

NOTICE TO COMPLY WITH REQUIREMENTS FOR PATENT APPLICATIONS CONTAINING NUCLEOTIDE SEQUENCE AND/OR AMINO ACID SEQUENCE DISCLOSURES

Applicant must file the items indicated below within the time period set the Office action to which the Notice is attached to avoid abandonment under 35 U.S.C. § 133 (extensions of time may be obtained under the provisions of 37 CFR 1.136(a)).

The nucleotide and/or amino acid sequence disclosure contained in this application does not comply with the requirements for such a disclosure as set forth in 37 C.F.R. 1.821 - 1.825 for the following reason(s):

☒ 1. This application clearly fails to comply with the requirements of 37 C.F.R. 1.821-1.825. Applicant's attention is directed to the final rulemaking notice published at 55 FR 18230 (May 1, 1990), and 1114 OG 29 (May 15, 1990). If the effective filing date is on or after July 1, 1998, see the final rulemaking notice published at 63 FR 29620 (June 1, 1998) and 1211 OG 82 (June 23, 1998).

☐ 2. This application does not contain, as a separate part of the disclosure on paper copy, a "Sequence Listing" as required by 37 C.F.R. 1.821(c).

☐ 3. A copy of the "Sequence Listing" in computer readable form has not been submitted as required by 37 C.F.R. 1.821(e).

☐ 4. A copy of the "Sequence Listing" in computer readable form has been submitted. However, the content of the computer readable form does not comply with the requirements of 37 C.F.R. 1.822 and/or 1.823, as indicated on the attached copy of the marked -up "Raw Sequence Listing."

☐ 5. The computer readable form that has been filed with this application has been found to be damaged and/or unreadable as indicated on the attached CRF Diskette Problem Report. A Substitute computer readable form must be submitted as required by 37 C.F.R. 1.825(d).

☐ 6. The paper copy of the "Sequence Listing" is not the same as the computer readable from of the "Sequence Listing" as required by 37 C.F.R. 1.821(e).

☒ 7. Other: Sequences in application not in Sequence Compliance (see Office Action).

Applicant Must Provide:

☒ An initial or substitute computer readable form (CRF) copy of the "Sequence Listing".

☒ An initial or substitute paper copy of the "Sequence Listing", as well as an amendment directing its entry into the specification.

☒ A statement that the content of the paper and computer readable copies are the same and, where applicable, include no new matter, as required by 37 C.F.R. 1.821(e) or 1.821(f) or 1.821(g) or 1.825(b) or 1.825(d).

For questions regarding compliance to these requirements, please contact:

For Rules Interpretation, call (703) 308-4216 or (703) 308-2923
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